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(54) Process for preparing crystalline loracarbef monohydrate

Verfahren zur Herstellung von kristallisiertem Loracarbef Monohydrat

Procédé de préparation du monohydrate de loracarbef cristallisé

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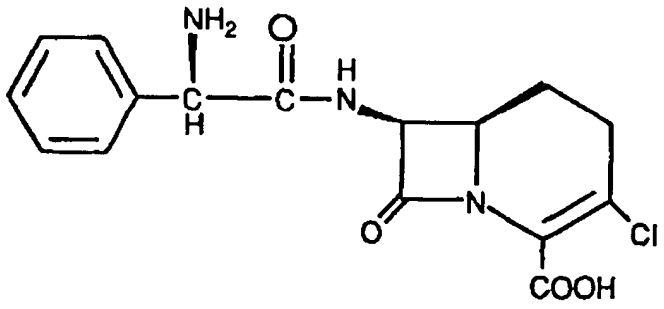
Description

This invention relates to a process for the preparation of a crystalline monohydrate form of a carbacephalosporin. The β-lactam antibiotic of the formula (I),



(I)

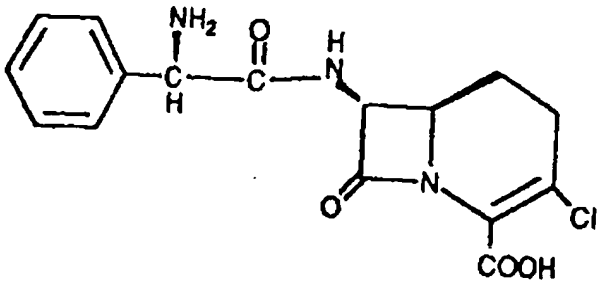
is the potent orally active antibiotic known as loracarbef. The antibiotic is described, for example by J. Hashimoto, *et al.*, in U.S. Patent No. 4,335,211, issued June 15, 1982.

The above compound comes in various forms, including the crystalline monohydrate form, which is disclosed in European Patent Publication 0,311,366 having a publication date of April 12, 1989. The crystalline dihydrate form of the compound is disclosed in European Patent Publication 369,686 published May 23, 1990. Other known solvate forms of the compound are disclosed in Eckrich *et al.*, U.S. Patent No. 4,977,257. As set out in the Eckrich *et al.* patent, the crystalline monohydrate form of loracarbef may be derived from the loracarbef bis(DMF)solvate. The procedure for such conversion involves dissolving the loracarbef bis(DMF)solvate in water, adding hydrochloric acid followed by triethylamine. The crystalline monohydrate is then filtered from the mixture. This particular process is hampered by the inefficient removal of residual dimethylformamide (present in the intermediate loracarbef bis(DMF)solvate), and triethylamine (used to crystallize loracarbef monohydrate) from the crystals slow filtration and wash difficulties.

It has been determined that loracarbef crystalline monohydrate, which is a fine "hair-like" crystal, apparently forms a mat on the filter medium which prevents or reduces the ability to remove the occluded solvent and base. In order to obtain acceptable levels of the DMF and triethylamine it has been necessary to wash the crystals with water one or more times. Since loracarbef monohydrate is moderately soluble in water (approximately 10 mg/ml) significant yield losses result when such reslurries are needed. Added to this is the slow filterability in general of the monohydrate.

In light of the above difficulties, what is needed is a process which avoids not only the need to use acids and bases to produce the monohydrate, but also avoids the requirement for filtration, requiring only a dry down to produce the monohydrate.

The invention provides a process for the preparation of the crystalline monohydrate form of the compound of the formula (I)



(I)

which comprises the step of mixing crystalline a form of loracarbef other than the crystalline monohydrate, selected from the ethanol crystal, acetone crystal, crystalline dihydrate, acetonitrile crystal, methanol crystal, propanol crystal, ethyl acetate crystal, methylene chloride crystal , and crystalline bis or mono(DMF) form of the compound of formula (I), in water at a temperature between about 30°C to about 60°C, and preferably at a temperature between 40°C and

50°C. Conversion may also be accomplished by exposing the loracarbef form to saturated steam at a temperature of between about 90° to about 100°C. One embodiment of the invention also comprises the preparation of the above mentioned crystal forms other than the crystalline monohydrate by slurrying the bis(DMF)solvate form of the compound of formula (I) with the respective solvent.

In order to find a process for preparing crystalline monohydrate with the desired characteristics, loracarbef dihydrate was slurried in water and heated to 50°C, without the addition of acid or base. Within minutes the dihydrate plates which were initially present converted to small hair-like crystals characteristic of the monohydrate. X-ray data later confirmed that indeed the monohydrate had been obtained by this route.

To see how general this conversion would be, loracarbef bis(DMF)solvate crystals were slurried in water at 50°C and these also converted to the monohydrate. However, the problem of residual DMF existed, as DMF has a relatively high boiling point (153°C)

This problem was circumvented by reslurrying loracarbef disolvate in ethanol, which has a much lower boiling point (78.5°C) which effectively displaces the dimethylformamide from the crystal, and forms an ethanol crystal form of loracarbef. This proved to be the key to converting the bis(DMF)solvate to the monohydrate in good yield and with acceptable quality. It was determined that acetone as well is able to displace the dimethylformamide. Experiments have shown this route was capable of giving good yields and acceptable product. Other organic solvents, such as methanol, isopropanol, propanol, ethyl acetate, methylene chloride and acetonitrile may also be used in the solvent exchange. Important characteristics for the solvent are that they be relatively volatile (Bp<100C) and are miscible in the system.

The crystal solvent forms of loracarbef are formed by slurrying the crystalline bis(DMF)solvate of the compound of formula (I) with the solvent, and without need of addition of acid or base. The amount of the solvent used should be about 50 ml to 100 ml per 7g of the DMF disolvate. It has been determined that ethanol and acetone can remove DMF with virtually no yield loss.

It should be understood, however, that the reslurry or steam conversion applies to intermediate forms containing solvents such as dimethylformamide (DMF), the advantage being the avoidance of using acids or bases to result in the crystalline monohydrate. Therefore, all forms of loracarbef may be used in these processes, the use of those forms with a low boiling point solvent being preferred.

The loracarbef forms, when slurried in water at a temperature between about 30°C to about 60°C, and preferably at a temperature between 40°C to 50°C, convert to an acceptable loracarbef monohydrate crystal without the need for addition of acid or base. Also, a conversion may be accomplished by purging saturated steam at a temperature of between about 90°C to 100°C through the loracarbef form.

Since the dihydrate can be more efficiently water washed than the monohydrate, a dihydrate intermediate can be crystallized to facilitate the removal of dimethylformamide and triethylamine (or other base) followed by the reslurry conversion to the monohydrate. Experiments using 50°C reslurry conversions are summarized in Table 1. In these experiments, a dihydrate, an ethanol crystal derived from DMF disolvate, and an acetone crystal derived from DMF disolvate, were converted to the monohydrate crystal. The residual DMF in the monohydrate slightly exceeded the desired limit, although subsequent experiments were able to achieve levels well below that limit.

Table 1

	Yield	*Anhydrous Potency*	*Related Subs*	*DMF*	*H_2O KF*
	%	%	%	%	%
Dihydrate	79.2	98.8	0.11	0.22	4.6
Ethanol Crystal	85.0	98.5	0.16	0.41	4.3
Acetone Crystal	81.3	98.7	0.16	0.22	4.6
Specifications		95-105	<2	<0.1	3.5-6.0

As the water reslurry step is primarily used to convert one crystal form to another and is not necessarily a purification step, this opens up several additional process advantages. The mother liquors may be recycled back to the reslurry process to be used instead of water alone, as the mother liquors would not contain acid or base as with the prior processes. This would eliminate the need for a second crop crystallization and also reduce yield losses since second crop yields are only about 80%. Therefore, when the term "water" is used, this includes water which may have other solvents or contaminants therein.

To take this a step further, another approach could be to dry down the final slurry and obtain an acceptable loracarbef monohydrate product. This would avoid the filtration of the crystalline monohydrate, also avoiding milling steps and second crops since, of course, no filtrate would be generated. Yields by this route should be almost quantitative. In the prior processes, acid and/or base is used to precipitate the monohydrate. As no acid or base is needed in this

water reslurry process, drying of the resulting monohydrate mixture, without need for precipitation and filtration, will result in an acceptable monohydrate.

Additionally, there is potential for the water reslurry conversion to be used in the pharmaceutical area for preparing a "ready to use" pediatric formulation. This is because loracarbef monohydrate, after drying and milling, no longer resembles the fine hair-like crystals prior to such manipulations. As such, the slurry characteristics are not as desirable, as compared to the original crystal monohydrate slurry which has a "milkshake" consistency and separates slowly. By using a precursor to the crystalline monodydrate, carrying out the water reslurry as part of the pediatric formulation process, it should be possible to retain the desired slurry characteristics.

Experimental Section

Example 1

Crystalline Monohydrate

Loracarbef dihydrate 10.0 g (7.7 bg) was slurried in 70 ml H_2O and the temperature was raised to 50°C. After ~10 minutes conversion appeared to be complete. The slurry was cooled to 25° and was harvested on a 7 cm Buchner funnel with Whatman filter 1. Filtration was slow. Mother liquor was used to rinse flask; ~5 ml H_2O wash was applied. The crystals were dried overnight in the vacuum oven at 45°C. Wgt: 7.29 g, Purity: 94.3% (98.8% anhydrous), DMF: 0.22%, KF: 4.6%, Rel. Subs: 0.11%, K^+: 0.5%, Cl^-: 0.5%, Yield: 89.2% X-ray analysis: monohydrate.

Example 2

Loracarbef Ethanol Crystal

Loracarbef bis(DMF)solvate(7.0 g, 5.0 bg) was slurried in 50 ml 3A EtOH for 15 minutes (no noticeable change under microscope). The crystals were filtered on a 5.5 cm Buchner funnel with a Whatman 1 filter (fast filtration). The crystals were washed with ~7 ml EtOH. The crystals were dried in the vacuum oven for two hours at 45°C. Wgt: 5.41 g, Purity: 94.5%, DMF: 2.73%, KF: 0.3%, Rel. Subs: 0.16%, Yield: 101.4%

Example 3

Ethanol Crystal to Loracarbef Monohydrate

Loracarbef ethanol crystal (3.5 g, 3.3 bg) was slurried in 25 ml H_2O and heated to 50°C. The slurry became thick and was diluted to about 40 ml with water. After ~30 minutes, monohydrate crystals appeared. The slurry was harvested on a 4.25 cm Buchner funnel with a Whatman 1 filter. Mother liquor was used to rinse flask, but no wash was applied. The crystals were dried in the vacuum oven ~7 hrs at 45°C. Wgt: 2.94 g, Purity: 94.3% (98.5% anhydrous), DMF: 0.41%, KF: 4.3%, Rel. Subs: 0.16%, Yield: 83.8%. X-ray analysis: Monohydrate.

Example 4

Loracarbef Acetone Crystal

Loracarbef DMF disolvate 7.0 g (5.0 bg) was slurried in 50 ml acetone for 15 minutes (no noticeable change under microscope). The crystals were filtered on a 5.5 cm Buchner funnel with a Whatman 1 filter (fast filtration). The crystals were washed with ~7 ml acetone. The crystals were dried in the vacuum oven for two hours at 45°C. Wgt: 5.66 g, Purity: 90.4%, DMF: 3.15%, KF: 4.3%, Rel. Subs: 0.23%, Yield: 101.5%

Example 5

Acetone Crystal to Loracarbef Monohydrate

Loracarbef acetone crystal (3.5 g, 3.2 bg) was slurried in 40 ml H_2O and heated to 50°C. After ~30 minutes crystals appeared. The slurry was harvested on a 4.25 cm Buchner funnel with a Whatman 1 filter. Mother liquor was used to rinse flask, but no wash was applied. The crystals were dried in the vacuum oven ~7 hrs at 45°C. Wgt: 2.69 g, Purity: 94.2% (98.7% anhydrous), DMF: 0.22%, KF: 4.6%, Rel. Subs: 0.16%, Yield: 80.1%
X-ray analysis: Monohydrate

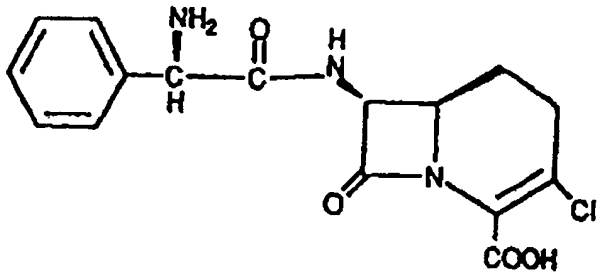
Example 6

Recycle of Monohydrate Mother Liquor for Reslurry of Ethanol Crystal

I. Loracarbef ethanol crystal (2.0 g, 1.95 bg) was reslurried in 35 ml H_2O and heated to 50°C. After ~20 minutes the material converted to monohydrate. The slurry was harvested on a 4.25 cm Buchner funnel with a Whatman 1 filter. The cake was washed with ~5 ml H_2O. The crystals were dried in the vacuum oven overnight at 45°C. Wgt: 1.61 g, Purity: 94.6% (98.9% anhydrous), DMF: 0.00%, KF: 4.3%, Related Subs: 0.14%, Yield: 80.0%
II. Loracarbef ethanol crystal (2.0 g 1.95 bg) was reslurried in the mother liquor from I and heated to 50°C. After ~20 minutes crystals converted to monohydrate. The slurry was harvested on a 4.25 cm Buchner funnel with a Whatman 1 filter. The cake was washed with ~5 ml H_2O. The crystals were dried in the vacuum oven overnight at 45°C. Wgt: 1.98 g, Purity: 94.5% (98.4% anhydrous), DMF: 0.01%, KF: 4.0%, Related Subs: 0.16%, Yield: 97.6%
III. Lorcarbef ethanol crystal (2.0 g, 1.95 bg) was reslurried in the mother liquor from II and heated to 50°C. After ~20 minutes crystals converted to monohydrate. The slurry was harvested on a 4.25 cm Buchner funnel with Whatman 1. The cake was washed with ~7 ml H_2O. The crystals were dried in the vacuum oven overnight at 45°C. Wgt: 1.94 g, Purity: 93.9% (98.0% anhydrous), DMF: 0.01%, KF: 4.2%, Related Subs: 0.15%, Yield: 95.1%
IV. Lorcarbef ethanol crystal (2.0 g, 1.95 bg) was reslurried in the mother liquor from III and heated to 50°C. After ~20 minutes crystals converted to monohydrate. The slurry was harvested on a 4.25 cm Buchner funnel with Whatman 1. The cake was washed with ~10 ml H_2O The crystals were dried in the vacuum oven overnight at 45°C. Wgt: 2.08 g, Purity: 93.9% (97.9% anhydrous), DMF: 0.02%, KF: 4.1%, Related Subs: 0.18%, Yield: 101.8%
V. Lorcarbef ethanol crystal (2.0 g, 1.95 bg) was reslurried in the mother liquor from IV and heated to 50°C. After ~20 minutes crystals converted to monohydrate. The slurry was harvested on a 4.25 cm Buchner funnel with Whatman 1. The cake was washed with ~5 ml H_2O The crystals were dried in the vacuum oven overnight at 45°C. Wgt: 1.94 g, Purity: 93.5% (97.7% anhydrous), DMF: 0.02%, KF: 4.3%, Related Subs: 0.13%, Yield: 94.6%

Claims

1. A process for the preparation of the crystalline monohydrate form of the compound of the formula (I):



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which comprises the step of

(a) mixing a crystalline form of the compound of formula (I), other than the crystalline monohydrate form, in water at a temperature between 30° to 60°C; or
(b) exposing a crystalline form of the compound of formula (I), other than the crystalline monohydrate form, to saturated steam at a temperature of between 90°C to 100°C, wherein the crystalline form is selected from the ethanol crystal, acetone crystal, crystalline dihydrate, acetonitrile crystal, methanol crystal, propanol crystal, ethyl acelate crystal, methylene chloride crystal, crystalline bis(DMF) or crystalline mono(DMF) form.

2. The process as recited in Claim 1 wherein the water temperature is between 40°C and 50°C.

3. The process as recited in Claim 2 wherein said form is ethanol crystal, acetone crystal, acetonitrile crystal, methanol crystal, propanol crystal, ethyl acetate crystal or methylene chloride crystal form.

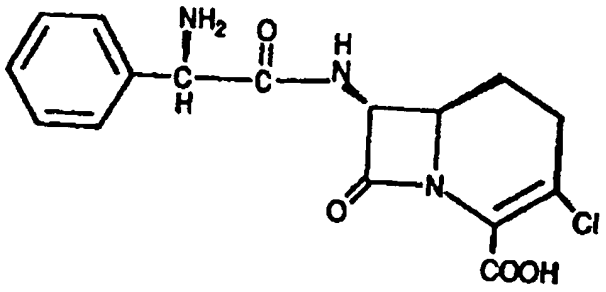
4. The process as recited in Claim 3 further comprising the step of forming the solvent crystal form of the compound by slurrying the crystalline bis(DMF) solvate form of the compound with the respective solvent.

5. The process as recited in Claim 4 wherein said solvent is ethanol or acetone.

6. The process as recited in Claim 1 further comprising the step of drying the crystalline monohydrate.

7. The process as recited in Claim 1 further comprising the step of filtering the crystalline monohydrate.

8. A process for the preparation of the crystalline monohydrate form of the compound of the formula (I):

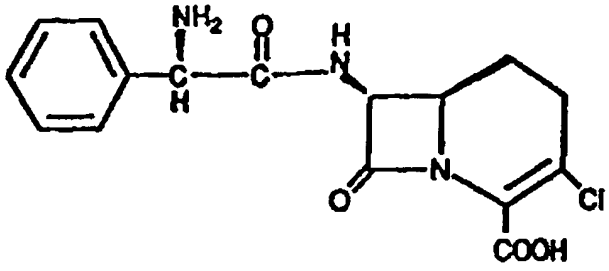


(I)

which comprises the step of mixing a crystalline form of the compound of formula (I), other than the crystalline monohydrate form, in water at a temperature between 30° to 60°C, wherein the crystalline form is selected from the ethanol crystal, acetone crystal, crystalline dihydrate, acetonitrile crystal, methanol crystal, propanol crystal, ethyl acetate crystal, methylene chloride crystal, crystalline bis(DMF) or crystalline mino(DMF) form.

Patentansprüche

1. Verfahren zur Herstellung der kristallinen Monohydratform der Verbindung der Formel (I)



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umfassend die Stufen, daß man

(a) eine andere kristalline Form der Verbindung der Formel (I) als die kristalline Monohydratform mit Wasser bei einer Temperatur von 30 bis 60°C vermischt, oder
(b) eine andere kristalline Form der Verbindung der Formel (I) als die kristalline Monohydratform gesättigtem Dampf bei einer Temperatur zwischen 90 und 100°C aussetzt,

wobei die kristalline Form ausgewählt ist aus Ethanolkristall, Acetonkristall, kristallinem Dihydrat, Acetonitrilkristall, Methanolkristall, Propanolkristall, Ethylacetatkristall, Methylenchloridkristall, kristalliner Bis-(DMF)- oder Mono-(DMF)-Form.

2. Verfahren nach Anspruch 1, worin die Wassertemperatur 40 bis 50°C ist.

3. Verfahren nach Anspruch 2, worin die Form Ethanolkristall-, Acetonkristall, Acetonitrilkristall-, Methanolkristall-, Propanokristall-, Ethylacetatkristall- oder Methylenchloridkristallform ist.

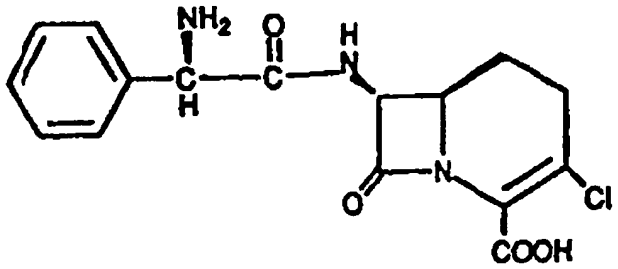
4. Verfahren nach Anspruch 3, weiter umfassend die Stufe, daß man die Lösungsmittelkristallform der Verbindung bildet, indem man die kristalline Bis-(DMF)-solvatform der Verbindung mit dem jeweiligen Lösungsmittel aufschlämmt.

5. Verfahren nach Anspruch 4, worin das Lösungsmittel Ethanol oder Aceton ist.

6. Verfahren nach Anspruch 1, weiter umfassend die Stufe, daß man das kristalline Monohydrat trocknet.

7. Verfahren nach Anspruch 1, weiter umfassend die Stufe, daß man das kristalline Monohydrat filtriert.

8. Verfahren zur Herstellung der kristallinen Monohydratform der Verbindung der Formel (I)



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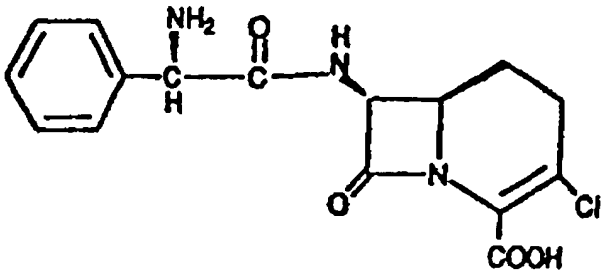
umfassend die Stufe, daß man eine andere kristalline Form der Verbindung der Formel (I) als die kristalline Monohydratform mit Wasser bei einer Temperatur von 30 bis 60°C vermischt, wobei die kristalline Form ausgewählt ist aus Ethanolkristall, Acetonkristall, kristallinem Dihydrat, Acetonitrilkristall, Methanolkristall, Propanolkristall, Ethylacetatkristall, Methylenchloridkristall, kristalliner Bis-(DNF)- oder Mono-(DMF)-Form.

Revendications

1. Procédé de préparation de la forme monohydrate cristalline du composé répondant à la formule (I)



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qui comprend l'étape de

(a) mélange d'une forme cristalline du composé répondant à la formule (I), autre que la forme monohydrate cristalline, dans l'eau à une température entre 30 °C et 60 °C; ou
(b) exposition d'une forme cristalline du composé répondant à la formule (I), autre que la forme monohydrate cristalline, à de la vapeur saturée à une température entre 90 °C et 100 °C,

la forme cristalline étant choisie parmi la forme cristalline d'éthanol, la forme cristalline d'acétone, la forme dihydrate cristalline, la forme cristalline d'acétonitrile, la forme cristalline de méthanol, la forme cristalline de propanol, la forme cristalline d'acétate d'éthyle, la forme cristalline de chlorure de méthylène, la forme bis(DMF) cristalline ou la forme mono(DMF) cristalline.

2. Procédé selon la revendication 1, dans lequel la température de l'eau se situe entre 40 °C et 50 °C.

3. Procédé selon la revendication 2, dans lequel ladite forme est la forme cristalline d'éthanol, la forme cristalline d'acétone, la forme cristalline d'acétonitrile, la forme cristalline de méthanol, la forme cristalline de propanol, la forme cristalline d'acétate d'éthyle ou la forme cristalline de chlorure de méthylène.

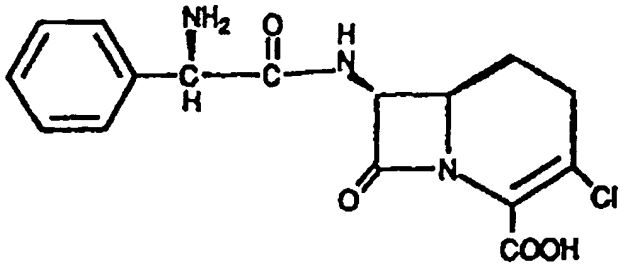
4. Procédé selon la revendication 3, comprenant en outre l'étape de formation de la forme cristalline de solvant du composé en mettant en suspension la forme solvate bis(DMF) du composé avec le solvant respectif.

5. Procédé selon la revendication 4, dans lequel ledit solvant est l'éthanol ou l'acétone.

6. Procédé selon la revendication 1, comprenant en outre l'étape de séchage du monohydrate cristallin.

7. Procédé selon la revendication 1, comprenant en outre l'étape de filtration du monohydrate cristallin.

8. Procédé de préparation de la forme monohydrate cristalline du composé répondant à la formule (I)



(I)

qui comprend l'étape de mélange d'une forme cristalline du composé répondant à la formule (I), autre que la forme monohydrate cristalline, dans l'eau à une température entre 30°C et 60°C, la forme cristalline étant choisie parmi la forme cristalline d'éthanol, la forme cristalline d'acétone, la forme dihydrate cristalline, la forme cristalline d'acétonitrile, la forme cristalline de méthanol, la forme cristalline de propanol, la forme cristalline d'acétate d'éthyle, la forme cristalline de chlorure de méthylène, la forme bis(DMF) cristalline ou la forme mono(DMF) cristalline.